Everything You Thought Was Atopic Dermatitis … That Wasn't

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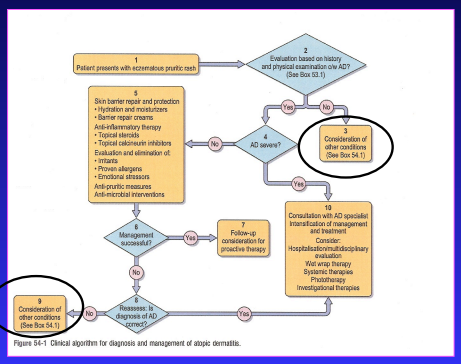
Disclosures

- Nothing relevant to this talk

Objectives

At the end of this session, participants will be able to:

1. Recognize diseases that may be misdiagnosed as atopic dermatitis
2. Discuss insights into pathophysiology of primary immunodeficiencies with eczema and aberrant IgE synthesis
3. Utilize appropriate testing in patients where the diagnosis of atopic dermatitis is in question



Boguniewicz M, et al. Pediatr Allergy 2010; 566

Differential diagnosis of AD

Congenital disorders
- Netherton's syndrome

Chronic dermatoses
- Seborrheic dermatitis
- Contact dermatitis (allergic or irritant)
- Nummular eczema
- Lichen simplex chronicus

Infections and infestations
- Scabies
- HIV-associated dermatitis

Malignancy
- Cutaneous T cell lymphoma (mycosis fungoides/Sézary syndrome)

Immunodeficiencies
- Wiskott-Aldrich syndrome
- SCID
- Hyper-IgE syndrome
- *DOCK8* mutations
- IPEX

Metabolic disorders
- Zinc deficiency
- Pyridoxine (vitamin B_6) and niacin deficiency
- Multiple carboxylase deficiency
- Phenylketonuria

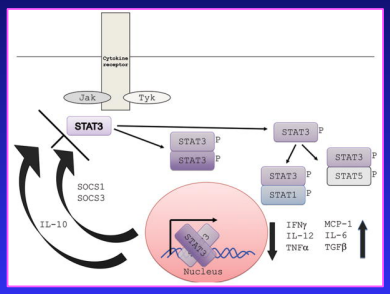
Proliferative disorder
- Letterer-Siwe disease

Hyper-IgE syndrome

- Multisystem disorder characterized by eczema, skin abscesses, recurrent staphylococcal infections of the skin and lungs, pneumatocele formation, candidiasis, eosinophilia, and elevated serum levels of IgE
- Nonimmunologic features of HIES include characteristic facial appearance, scoliosis, retained primary teeth, joint hyperextensibility, bone fractures after minimal trauma, and craniosynostosis
- Heterozygous mutations in signal transducer and activator of transcription 3 (*STAT3*) transmitted as autosomal dominant trait shown to be a cause of HIES (~60-70% cases)
- *STAT3* crucial for IL-6 mediated regulation of TH17 cells that are significant source of IL-17, a proinflammatory cytokine involved in host defense vs *S. aureus* and Candida

Woellner C, et al. J Allergy Clin Immunol 2010;125:424

STAT3 signaling pathway



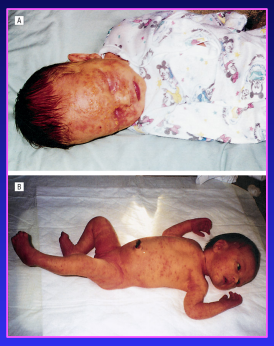
Freeman AF, et al. Pediatr Res 2009;65:32

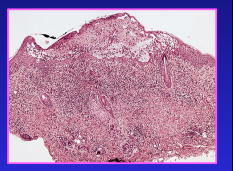
Features including cardinal features of HIES

	all HIES		HIES STAT3 wild-type		HIES STAT3 mutated	
	No.	%	No.	%	No.	%
Recurrent pneumonia	85/100	85	24/36	66.7	61/64	95.3
Eczema	90/100	90	32/36	88.9	58/64	90.6
Recurrent skin abscesses	86/100	86	28/36	77.8	58/64	90.6
Characteristic face	82/99	82.8	24/35	68.6	58/64	90.6
Failure to shed deciduous teeth	60/86	68.9	16/31	51.6	44/55	80.0
Lung cyst formation	61/97	62.9	14/34	41.2	47/63	74.6
Eosinophilia	68/94	72.3	27/36	75.0	41/58	70.7
Newborn rash	52/86	60.5	15/29	51.7	37/57	64.9
Other unusual infections	47/94	50	13/34	38.2	34/60	56.7
Increased interalar distance	37/83	44.6	10/31	32.3	27/52	51.9
Cathedral palate	41/84	48.8	12/31	38.7	29/53	54.7
Hyperextensibility	37/87	42.5	8/32	25.0	29/55	52.7
Pathologic bone fractures	32/94	34.0	5/35	14.3	27/59	45.8
Recurrent upper respiratory infections	41/92	44.6	14/33	42.4	27/59	45.8
Candidiasis	37/91	40.6	12/33	36.4	25/58	43.1
Scoliosis	20/83	24.1	7/33	21.2	13/50	26.0
Midline anomaly	12/86	14.0	5/34	14.7	7/52	13.5

Woellner C, et al. J Allergy Clin Immunol 2010;125:424

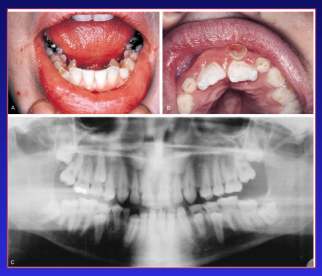
Grimbacher B, et al. N Engl J Med 1999;340:692





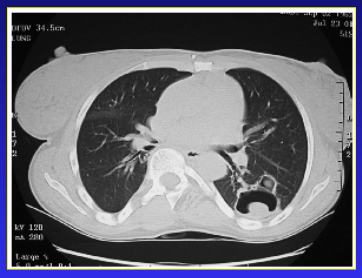
Intraepidermal eosinophilic pustule

Eberting CL, et al. Arch Dermatol 2004;140:1119



Grimbacher B, et al. N Engl J Med 1999;340:692

Pneumatocoeles with aspergilloma in HIES



Freeman AF, et al. J Allergy Clin Immunol 2007;119:1234

NIH Scoring HIE

Scoring System with Clinical and Laboratory Tests for Individuals in Kindreds with HIES

Clinical Findings	Points* 0	1	2	3	4	5	6	7	8	10
Highest serum-IgE level (IU/ml)†	<200	200–500			501–1,200				1,001–2,000	>2,000
Skin abscesses	None		1–2		3–4				>4	
Pneumonia (episodes over lifetime)	None		1		2		3			
Parenchymal lung anomalies	Absent						Bronchiectasis		Pneumatocele	
Retained primary teeth	None	1	2		3				>3	
Scoliosis, maximum curvature	<10°		10–14°		15°–20°				>20°	
Fractures with minor trauma	None				1–2				>2	
Highest eosinophil count (cells/μl)†	<700			700–800			>800			
Characteristic face	Absent		Mildly present			Present				
Midline anomaly‡	Absent					Present				
Newborn rash	Absent				Present					
Eczema (worst stage)	Absent	Mild	Moderate		Severe					
Upper respiratory infections per year	1–2	3	4–6		>6					
Candidiasis	None	Oral	Fingernails		Systemic					
Other serious infections	None				Severe					
Fatal infection	Absent				Present					
Hyperextensibility	Absent				Present					
Lymphoma	Absent				Present					
Increased nasal width§	<1 SD	1–2 SD		>2 SD						
High palate	Absent		Present							
Young-age correction	>5 years			2–5 years		1–2 years		<1 year		

≥15 likely HIES
≤ 10 unlikely HIES

Grimbacher B, et al. Am J Hum Genet 1999;65:735

Clinical presentation of patients with and without *STAT3* mutations

Findings	Patients with *STAT3* mutation (n = 48)	Patients without *STAT3* mutation (n = 30)
Increases serum IgE levels*	96%	97%
Blood eosinophilia	93%	77%
Eczema	98%	90%
Newborn rash	74%	40%
Skin abscesses	85%	37%
Internal abscesses	46%	0%
Pneumonia	94%	53%
Pneumatoceles	48%	3%
Susceptibility to infections	89%	70%
Severe infections#	35%	0%
Oral candidiasis	56%	24%
Nail/mucocutaneous candidiasis	54%	13%
Pathologic second dentition	79%	19%
Pathologic bone fractures	60%	3%
Scoliosis	42%	3%
Hyperextensible joints	60%	23%
Characteristic face	90%	17%
Broad nasal bridge	79%	22%
High palate	59%	22%
Atopic disease besides eczema	57%	88%
NIH score ≥40 points	96%	10%

*Serum IgE levels increased 10 times above the mean of age-matched control subjects.
#Sepsis, meningitis, osteomyelitis.

Schimke LF, et al. J Allergy Clin Immunol 2010;126:611

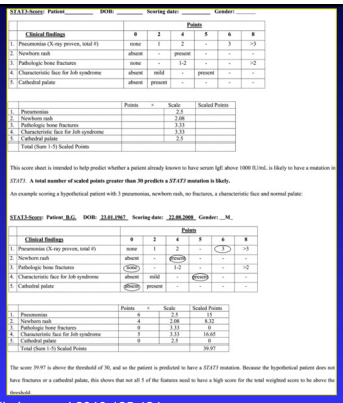
Sensitivity and specificity of clinical findings in patients with HIES and *STAT3* mutations

Findings	Sensitivity (%)	Specificity (%)
Increased serum IgE levels (>10 times normal)	95.8	3.3
Blood eosinophilia	93.5	23.3
Eczema	97.9	10
Newborn rash	73.9	60
Skin abscesses	85.4	63.3
Internal abscesses	45.8	100
Pneumonia	93.8	46.7
Pneumatoceles	47.9	96.7
Increased susceptibility to infections	89.4	30
Severe infections	34.8	100
Oral candidiasis	56.3	74.1
Nail/mucocutaneous candidiasis	54.2	86.7
Pathologic second dentition	78.6	75
Fractures without adequate trauma	60.4	96.7
Scoliosis	41.7	96.7
Hyperextensible joints	59.6	76.7
Characteristic facies*	95.8	60
Positive family history of HIES	6	100
Additional atopic findings	57.1	11.5

*Characteristic facial features, wide nose, and high palate.

Schimke LF, et al. J Allergy Clin Immunol 2010;126:611

Predicting *STAT3* mutation



STAT3-Score: Patient_____ DOB: _____ Scoring date: _____ Gender: _____

	Clinical findings	Points 0	2	4	5	6	8
1.	Pneumonias (X-ray proven, total #)	none	1	2	-	3	>3
2.	Newborn rash	absent	-	present	-	-	-
3.	Pathologic bone fractures	none	-	1-2	-	-	>2
4.	Characteristic face for Job syndrome	absent	mild	-	present	-	-
5.	Cathedral palate	absent	present	-	-	-	-

		Points	×	Scale	Scaled Points
1.	Pneumonias			2.5	
2.	Newborn rash			2.08	
3.	Pathologic bone fractures			3.33	
4.	Characteristic face for Job syndrome			3.33	
5.	Cathedral palate			2.5	
	Total (Sum 1-5) Scaled Points				

This score sheet is intended to help predict whether a patient already known to have serum IgE above 1000 IU/mL is likely to have a mutation in *STAT3*. **A total number of scaled points greater than 30 predicts a *STAT3* mutation is likely.**

An example scoring a hypothetical patient with 3 pneumonias, newborn rash, no fractures, a characteristic face and normal palate:

STAT3-Score: Patient_H.G. DOB: 23.01.1967 Scoring date: 22.08.2008 Gender: _M_

	Clinical findings	Points 0	2	4	5	6	8
1.	Pneumonias (X-ray proven, total #)	none	1	2	-	(3)	>3
2.	Newborn rash	absent	-	(present)	-	-	-
3.	Pathologic bone fractures	(none)	-	1-2	-	-	>2
4.	Characteristic face for Job syndrome	absent	mild	-	(present)	-	-
5.	Cathedral palate	(absent)	present	-	-	-	-

		Points	×	Scale	Scaled Points
1.	Pneumonias	6		2.5	15
2.	Newborn rash	4		2.08	8.32
3.	Pathologic bone fractures	0		3.33	0
4.	Characteristic face for Job syndrome	5		3.33	16.65
5.	Cathedral palate	0		2.5	0
	Total (Sum 1-5) Scaled Points				39.97

The score 39.97 is above the threshold of 30, and so the patient is predicted to have a *STAT3* mutation. Because the hypothetical patient does not have fractures or a cathedral palate, this shows that not all 5 of the features need to have a high score for the total weighted score to be above the threshold

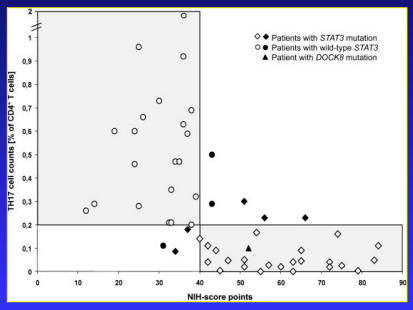
Woellner C, et al. J Allergy Clin Immunol 2010;125:424

Diagnostic guidelines for *STAT3*-mutant HIES

- Possible: IgE > 1000 IU/mL & weighted score of clinical features >30 based on recurrent pneumonia, newborn rash, pathologic bone fractures, characteristic face and high palate
- Probable: These characteristics & lack of TH17 cells or family history for definitive HIES
- Definitive: These characteristics & dominant-negative heterozygous mutation in *STAT3*

Woellner C, et al. J Allergy Clin Immunol 2010;125:424

Correlation of NIH score, TH17 cells & *STAT3* mutation status



Schimke LF, et al. J Allergy Clin Immunol 2010;126:611

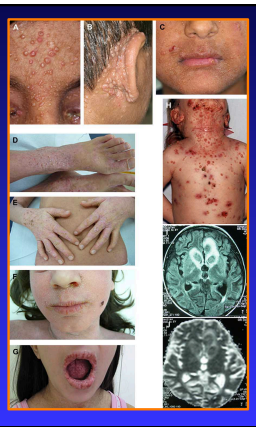
Dedicator of cytokinesis 8

- *DOCK8* encodes a protein implicated in the regulation of the actin cytoskeleton
- Susceptibility to viral infections, defective CD4+ and CD8+T-cell activation and TH17 cell differentiation, impaired eosinophil homeostasis and dysregulation of IgE, eczema
- Mutations in *DOCK8* are responsible for many cases of AR HIE syndrome

Englehardt KR , et al. J Allergy Clin Immunol 2009;124:1289

DOCK8 mutations

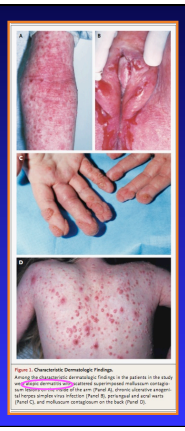
Molluscum contagiosum,
Human papilloma virus,
encephalitis



Englehardt KR , et al.
J Allergy Clin Immunol 2009;124:1289

DOCK8 mutations

Herpes simplex virus,
Human papilloma virus,
Molluscum contagiosum



Zhang Q, et al. N Engl J Med 2009;361

FOXP3 & IPEX syndrome

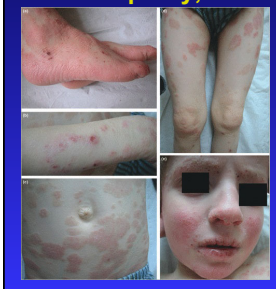
- Mutations of forkhead box protein 3 (*FOXP3*) the master gene for naturally occurring regulatory T cells (nTregs) are responsible for the impaired function of nTregs, resulting in immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome

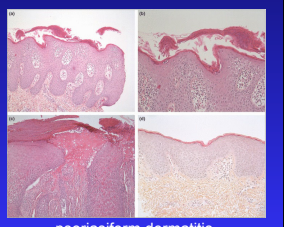
Dermatologic and immunologic findings in the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare genodermatosis associated with dermatitis, enteropathy, type 1 diabetes, thyroiditis, hemolytic anemia, and thrombocytopenia
- IPEX results from mutations of *FOXP3*, a gene located on the X chromosome that encodes a DNA-binding protein required for development of regulatory T cells

Nieves DS, et al. Arch Dermatol 2004;140:466

Cutaneous manifestations of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome

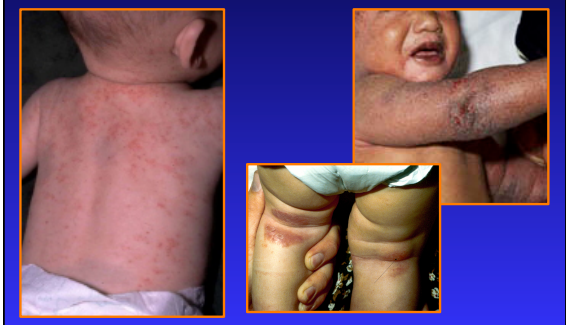




psoriasiform dermatitis

Halabi-Tawil M, et al. Br J Dermatol 2009;160:645

Wiskott-Aldrich syndrome



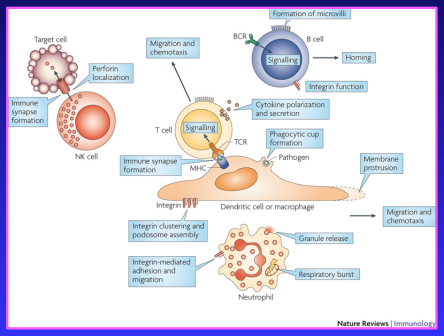
Eczema & petechiae & hemorrhage

Wiskott-Aldrich syndrome

- X-linked inheritance with mutations in the *WAS* gene
- WASP encoded by *WAS* gene is a multifunctional signaling element expressed in immune and hematopoietic cells that plays a critical role in cytoskeletal reorganization, immune synapse formation and intracellular signaling
- Affected boys in classic presentation with hemorrhagic diathesis 2° to thrombocytopenia, bacterial, viral & fungal infections and eczema

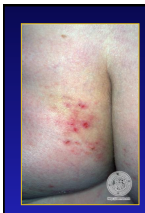
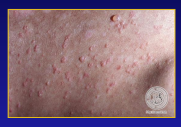
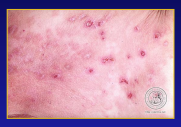
Albert MH, et al. Curr Opin Hematol 2011;18:42

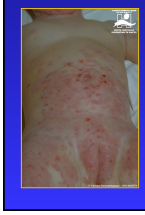
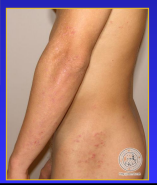
WASP function in immune cells



Thrasher AJ, et al. Nature Rev Immunol 2010;10

Dermatitis herpetiformis

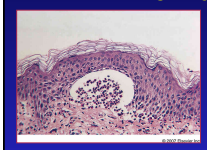
Dermatitis herpetiformis

- Autoimmune blistering disease with classical presentation characterized by intensely pruritic polymorphous lesions symmetrically located on extensor surfaces with concentration on the elbows, knees, scapulae, shoulders, sacrum, hairline, and scalp
- Papillary dermal neutrophilic microabscesses seen on routine biopsy and similar distribution of granular deposition of IgA on DIF confirms diagnosis
- Nearly all patients will have clinical or subclinical evidence of small bowel villous atrophy as DH is the cutaneous manifestation of gluten-sensitive enteropathy associated with HLA DQ2 & 8

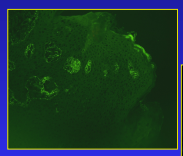
Junkins-Hopkins JM. J Am Acad Dermatol 2010;63:526

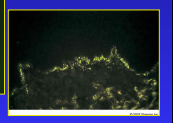
- Both conditions caused by immunologic reaction to ingested gliadin found in wheat, rye, barley and both associated with circulating IgA antibodies against endomysium and tissue transglutatminase (tTG)
- Patients with DH also have IgA antibodies directed against epidermal transglutaminase (eTG), which is homologous to tTG
- A population of non–cross reactive anti-eTG IgA antibodies are found only in DH patients, suggesting that eTG is the target in DH

Dermatitis herpetiformis



Neutrophilic microabscesses in dermal papillae

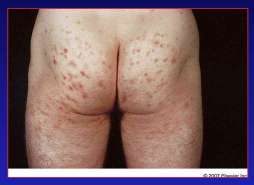




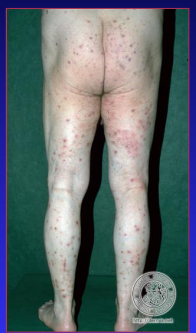
Granular IgA

Unusual presentations of DH

- Although name reflects clinical presentation of herpetiform vesicles, these are often immediately excoriated, resulting in erosions, crusted papules or areas of postinflammatory dyschromia, or pts may have erythema, urticarial plaques or papules
- Severe pruritus, burning and/or stinging, alone or preceding the eruption by 8 to 12 hours are often presenting symptoms simulating scabies
- DH usually occurs in patients between 20 and 40 years of age, but the condition is not restricted to adults
- Children with recalcitrant eczematous lesions, pruritic impetigo and papular urticaria may have DH



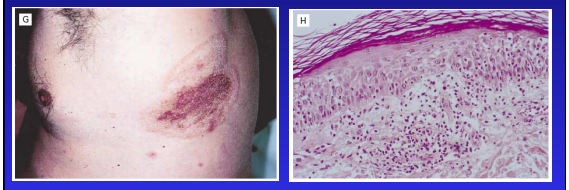
Dermatitis herpetiformis



Scabies!

Mycosis fungoides happens…

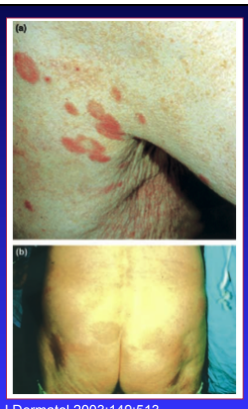
- The most common form of CTCL
- Epidermotropic neoplasm of CD4+ T cells



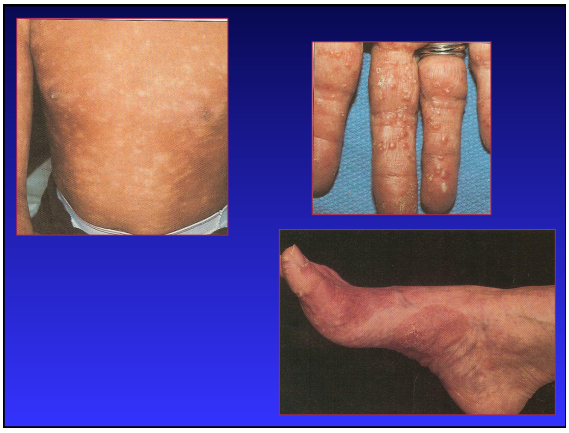
Robert C, Kupper TS. N Engl J Med 1999;341:1817

Cutaneous T cell lymphoma

- Mycosis fungoides - skin is variably affected by flat patches, thin plaques or tumors - is the most common form of CTCL
  - Patch or plaque lesions have a predilection for non sun-exposed areas (e.g., the buttocks, medial thighs, and breasts), although any area of the skin may be affected
  - Insidious in onset, not uncommon to go unrecognized for # years, most often misdiagnosed as chronic contact dermatitis, atopic dermatitis, or psoriasis
  - Lesions may become variably thickened, may coalesce to form larger plaques, or may undergo partial involution, leaving residual annular plaques
  - Patches and plaques may show hypopigmentation or hyperpigmentation, atrophy, and petechiae

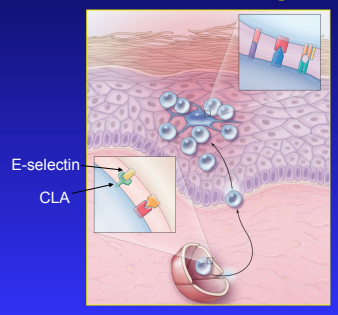


Stevens SR, et al. Br J Dermatol 2003;149:513



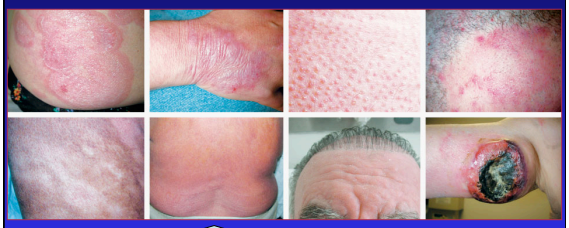
- Lymphocytic infiltrate in superficial dermis with individual lymphocytes among epidermal keratinocytes defines epidermotropism that characterizes this lymphoma
- Clustering of clonal T cells around Langerhans cells (Pautrier's microabscesses) suggests dependence of T cells on interactions with these DCs
- Lymphocytes may show varying degrees of atypia (pleomorphic, hyperchromatic or convoluted nuclei)
- In addition to routine H&E, staining of skin-biopsy specimens with a panel of lymphocyte markers helps define malignant clone for subclassification (MF positive for T-cell receptor γ/δ associated with more aggressive disease than MF without receptor rearrangement)

MF with skin-homing T cells



Girardi M, et al. N Engl J Med 2004;350:1978

Cutaneous manifestations of MF

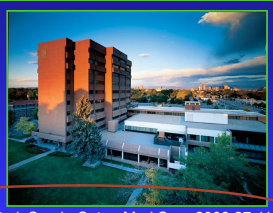


Erythrodermic MF

Girardi M, et al. N Engl J Med 2004;350:1978

- Examination of multiple biopsy specimens from various lesions at various times will increase the likelihood that an accurate diagnosis will be made and PCR analysis of T-cell receptor genes to determine clonality may also be helpful

Atopic Dermatitis Program 1990-2012



Boguniewicz M, et al. Semin Cutan Med Surg 2008;27:115